



## LETTER TO THE EDITOR

# Re: Measurement of Chimerism After Hematopoietic Stem Cell Transplantation

We would like to congratulate Drs. Antin et al. on their thorough and practical review of mixed chimerism after hematopoietic stem cell transplantation (HSCT) [1]. We agree that frequent measurements of hematopoietic chimerism are warranted after transplantation. We also agree with the recommendation to use more accurate variable number tandem repeats (VNTR) or short tandem repeats (STR) analyses to evaluate hematopoietic chimerism. Antin and colleagues clearly delineate the decision-making process for malignant disease. In contrast, the levels of mixed chimerism necessary for effective correction in the setting of nonmalignant disease are less clear. The authors suggest that levels of chimerism in excess of 10% are required for correction of the nonmalignant disease phenotype. However, they proceed to recommend that donor levels of 3% to 10% are sufficient for correction in the context of sickle cell disease (SCD).

This recommendation is at odds with recent human and animal studies of SCD. Unfortunately, insights into the requirements sufficient for functional correction of the human disease phenotype have been based on studies involving anecdotal observations in a small number of patients undergoing matched sibling allografts after myeloablative chemotherapy. In this context, the lowest reported degree of stable donor hematopoietic chimerism found to correct SCD is approximately 11% donor cells sustained over 6 years after matched sibling allograft using an HbAA donor. The patient who underwent this treatment has demonstrated a hemoglobin S of approximately 7% on serial hemoglobin electrophoreses (M. Walters, personal communication). Similar studies suggest that a higher level of chimerism, 30% to 40%, is required if HbAS donors are used. Elegant studies in an animal model of SCD confirm the necessity of a similar level of correction of HbS levels. Indeed, these studies suggest that higher levels of donor chimerism ( $\geq 20\%$ ) may be required to retard or correct the silent organ pathology characteristic of SCD [2]. Interestingly, human and animal studies of  $\beta$ -thalassemia, a related hemoglobinopathy, confirm the 10% threshold [3].

Further transplantation trials will be required to establish a firm recommendation on the degree of donor chimerism required for correction of the circulating HbS levels and the

organ damage inherent to this disease. Measurement of lineage-specific chimerism will be particularly helpful in this context, yielding more precise information than routine marrow or peripheral blood analyses. Finally, it is possible that the use of alternate donor grafts in SCD will make it necessary to modify the donor chimerism threshold, this threshold modification depending in part on donor source, graft engineering, and the conditioning regimen used.

In summary, the evidence to date suggests that donor cell engraftment of greater than 10% is required for effective treatment of patients with sickle cell disease in the context of hemoglobin AA donors. A similar level is required for treatment of  $\beta$ -thalassemia. Levels of donor hematopoietic chimerism perhaps as high as 30% to 40% may be required for SCD patients with hemoglobin AS donors.

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## REFERENCES

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3. Persons DA, Allay ER, Sabatino DE, Kelly P, Bodine DM, Nienhuis AW. Functional requirements for phenotypic correction of murine  $\beta$ -thalassemia: implications for human gene therapy. *Blood*. 2001; 97:3275-3282.